1.1.1. ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of PegIntron, powder for solution for injection contains 50 micrograms of peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol).
Each vial provides 50 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PegIntron is indicated in monotherapy in case of intolerance or contraindication to ribavirin, for the treatment of adult patients with histologically proven chronic hepatitis C who have serum markers for virus C replication, e.g. those who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV.

The optimal treatment for chronic hepatitis C is considered to be the administration of a combination of interferon alfa-2b with ribavirin.
The safety and efficacy of the combination of PegIntron and ribavirin has not yet been documented.

4.2 Posology and method of administration

PegIntron treatment should be initiated only by a physician experienced in the treatment of patients with hepatitis C.

PegIntron monotherapy is administered subcutaneously at a dose of 0.5 or 1.0 microgram/kg once weekly for at least 6 months. The dose should be selected based on the anticipated efficacy and

safety (see** 4.8 **and** 5.1**). In patients showing loss of HCV-RNA at 6 months, treatment is continued for an additional 6 months, i.e.1 year of treatment.

If adverse events develop during the course of treatment, it is recommended that the dose of PegIntron be modified to one-half the starting dose once weekly. If persistent or recurrent intolerance develops following dose adjustment, discontinue treatment with PegIntron.

Dose reduction is recommended if the neutrophil count is < 0.75 x 10^9/l or if the platelet count is < 50,000 x 10^9/l. Discontinuation of treatment is recommended if the neutrophil count is < 0.50 x 10^9/l or if the platelet count is < 25,000 x 10^9/l.

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment (creatinine clearance ≤ 50 ml/minute) (see **5.2**). It is recommended that these patients be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in hepatic impairment: The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- ***Hypersensitivity to the active substance or to any of the excipients;***
- ***Hypersensitivity to any interferon;***
- Autoimmune hepatitis or a history of autoimmune disease;
- Pre-existing severe psychiatric condition or a history of severe psychiatric disorder;
- ***Pre-existing thyroid abnormalities for which thyroid function cannot be maintained in the normal range by medication;***
- Severe renal or hepatic dysfunction;
- Epilepsy and/or compromised central nervous system (CNS) function;
- Pregnancy.

4.4 Special warnings and special precautions for use

Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been rarely observed during interferon alfa-2b therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Liver function: Discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

*Debilitating medical conditions****: PegIntron must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.***

*Pulmonary changes****: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. The aetiology has not been defined. These symptoms have been reported more frequently in patients treated with interferon alpha when shosaikoto, a Chinese herbal medicine, is administered concomitantly. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.***

*Autoimmune disease**: The development of auto-antibodies has been reported during treatment with alpha interferons. Clinical manifestations of autoimmune disease during interferon therapy may occur more frequently in patients predisposed to the development of autoimmune disorders.***

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons. Any patient complaining of loss of visual acuity or visual field must have an eye examination. Because these ocular events may occur in conjunction with other disease states, a visual exam prior to initiation of PegIntron therapy is recommended in patients with diabetes mellitus or hypertension.

Psychiatric and Central Nervous System (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy. Other CNS effects manifested by confusion and other alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PegIntron therapy.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alfa-2b have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using interferon alfa-2b 2.8 % patients overall developed thyroid abnormalities. These were controlled by conventional therapy for thyroid dysfunction. The mechanism by which alpha interferons may alter thyroid status is unknown. Prior to initiation of PegIntron therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. PegIntron treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

*Other**: Due to reports of interferon alfa-2b exacerbating pre-existing psoriatic disease, use of PegIntron in patients with psoriasis is recommended only if the potential benefit justifies the potential risk.***

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function are recommended in all patients prior to and periodically during treatment with PegIntron. Acceptable baseline values that may be considered as a guideline are:

- Platelets ≥ 100,000/mm^3
- Neutrophil count ≥ 1,500/mm^3
- Thyroid Stimulating Hormone (TSH) level must be within normal limits

4.5 Interaction with other medicinal products and other forms of interaction

Results of a single-dose study with PegIntron demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50 % reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. PegIntron should not be used during pregnancy (see **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

It is not known whether the components of this medicinal product are excreted in human milk. Therefore, a decision must be made whether to discontinue treatment or discontinue nursing, taking into account the importance of the treatment to the mother.

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

Based on a clinical database of 940 PegIntron treated patients of whom 754 received 0.5 to 1.5 microgram/kg for a year, most undesirable effects were mild or moderate in severity and not treatment limiting.

Table 1 Adverse events reported very commonly in clinical trials (≥ 10 % of patients)			
	PegIntron 0.5 microgram/kg once weekly N=315	PegIntron 1.0 microgram/kg once weekly N=297	IntronA 3 MIU three times a week N=303
Application Site Disorders			
Inflammation	44 %	42 %	16 %
Reaction	7 %	10 %	5 %
General Body Discomfort			
Asthenia	12 %	12 %	11 %
Dizziness	8 %	12 %	10 %
Fatigue	43 %	51 %	50 %
Fever	31 %	45 %	30 %
Headache	61 %	64 %	58 %
Flu-like Symptoms	18 %	22 %	19 %
Rigors	34 %	40 %	33 %
Weight Decrease	10 %	11 %	13 %
Gastro-intestinal			
Anorexia	10 %	20 %	17 %
Nausea	21 %	26 %	20 %
Diarrhoea	16 %	18 %	16 %
Abdominal Pain	14 %	15 %	11 %
Musculoskeletal			
Pain	19 %	28 %	22 %
Myalgia	48 %	54 %	53 %
Arthralgia	26 %	25 %	27 %
Psychiatric			
Depression	27 %	29 %	25 %
Anxiety	10 %	9 %	10 %
Concentration Impaired	10 %	10 %	8 %
Insomnia	17 %	23 %	23 %
Irritability	19 %	18 %	24 %
Alopecia	20 %	22 %	22 %
Pharyngitis	12 %	10 %	7 %

Commonly reported undesirable effects (≥ 2 % of patients) were pruritus, skin dry, malaise, sweating increased, right upper quadrant pain, neutropaenia, rash, vomiting, mouth dry, emotional lability, nervousness, dyspnoea, viral infection, somnolence, thyroid disorders, chest pain, dyspepsia, flushing, paresthaesia, coughing, agitation, sinusitis, hypertonia, hyperesthaesia, vision blurred, confusion, flatulence, libido decreased, erythema, eye pain, apathy, hypoesthaesia, loose stool, conjunctivitis, nasal congestion, constipation, vertigo, menorrhagia, menstrual disorder.

Rarely reported events include suicidal ideation and attempted suicide, hearing and retinal disorders, diabetes, hepatopathy and arrhythmia.

Granulocytopaenia (< 0.75 x 10^9/l) occurred in 4 and 7 % and thrombocytopaenia (< 70 x 10^9/l) in 1 and 3 % respectively of patients receiving 0.5 or 1.0 microgram/kg of PegIntron.

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators, Interferons, Peginterferon alfa-2b, ATC code: L03A B10.

PegIntron is a covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol. The average molecular weight of the molecule is approximately 31,300 daltons.

1.1.1.1. Interferon alfa-2b

Recombinant interferon alfa-2b is obtained from a clone of *E. coli*, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

In vitro and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

1.2. PegIntron

PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of Week 4 correlated with the dose of PegIntron.

1.3. PegIntron clinical trial results

The safety and efficacy of 48 weeks of treatment with 3 doses of PegIntron (0.5, 1.0, and 1.5 micrograms/kg administered subcutaneously once weekly) vs. IntronA (3 million IU administered subcutaneously 3 times a week) were studied in 1,219 treatment-naive patients with chronic hepatitis C. Table 2 provides sustained virologic response (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

Table 2 Proportion of patients with sustained loss of HCV

(%) of patients

	A	B	C	D	p Value**
Response*	PegIntron 0.5 micro-gram/kg N=315	PegIntron 1.0 micro-gram/kg N=297	PegIntron 1.5 micro-grams/kg N=304	IntronA 3 MIU N=303	*A vs D B vs D C vs D*
Sustained Response 6 Months Post	57 (18 %)	73 (25 %)	71 (23 %)	37 (12 %)	0.042 < 0.001 < 0.001

Treatment					
* Serum HCV-RNA is measured by quantitative polymerase chain reaction with a lower limit of detection of 100 copies/ml (National Genetics Institute, Culver City, CA) ** Chi-square Test					

Table 3 Sustained Virologic Response by HCV Virus Level (copies/ml) and Genotype				
	Number (%) of Subjects			
	PegIntron 0.5 µg/kg	PegIntron 1.0 µg/kg	PegIntron 1.5 µg/kg	IntronA 3 MIU
Genotype 1				
≤ 2 million	14/52 (27)	16/42 (38)	19/56 (34)	10/48 (21)
> 2 million	8/159 (5)	12/157 (8)	12/167 (7)	4/169 (2)
Genotypes 2/3				
≤ 2 million	14/24 (58)	13/21 (62)	15/22 (68)	9/25 (36)
> 2 million	17/64 (27)	26/62 (42)	21/51 (41)	14/56 (25)

In general, most side effects were dose-related, and the Quality of Life was less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of IntronA three times a week (see also **4.8**).

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.
Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean PegIntron elimination half life is approximately 30.7 hours (range 27-33 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been

fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see **4.2**).

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors**: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.**

5.3 Preclinical safety data

Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to 4 weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential.

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

Solvent for parenteral use: water for injections

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also **6.6**).

6.3 Shelf life

2 years

After reconstitution:

- ***Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.***
- ***From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.***

6.4 Special precautions for storage

Store at 2°C - 8°C

6.5 Nature and contents of container

The powder is contained in a 2 ml vial, Type I flint glass, with a butyl rubber stopper in an aluminium flip-off seal with a polypropylene bonnet. The solvent is presented in a 2 ml ampoule, Type I flint glass.

PegIntron 50 micrograms is supplied as:

- ***1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;***
- ***1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;***
- ***4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;***
- ***4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;***
- ***6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use.***

6.6 Instructions for use and handling, and disposal

PegIntron is supplied as a powder of peginterferon alfa-2b at a strength of 50 micrograms for single use. Each vial must be reconstituted with 0.7 ml of water for injections for administration of up to 0.5 ml of solution. The reconstituted solution has a concentration of 50 micrograms/0.5 ml.

Using a sterilised injection syringe and injection needle, inject 0.7 ml of water for injections into the vial of PegIntron. Agitate gently to complete dissolution of powder. The appropriate dose can then be withdrawn with a sterilised injection syringe and injected.

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. Do not use if discolouration is present. Discard any unused material.

7. MARKETING AUTHORISATION HOLDER

SP Europe

73, rue de Stalle

B-1180 Bruxelles

Belgium

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80 micrograms powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of PegIntron, powder for solution for injection contains 80 micrograms of peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol).
Each vial provides 80 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

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4.1 Therapeutic indications

PegIntron is indicated in monotherapy in case of intolerance or contraindication to ribavirin, for the treatment of adult patients with histologically proven chronic hepatitis C who have serum markers for virus C replication, e.g. those who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV.

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PegIntron treatment should be initiated only by a physician experienced in the treatment of patients with hepatitis C.

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safety (see** 4.8 **and** 5.1**). In patients showing loss of HCV-RNA at 6 months, treatment is continued for an additional 6 months, i.e.1 year of treatment.

If adverse events develop during the course of treatment, it is recommended that the dose of PegIntron be modified to one-half the starting dose once weekly. If persistent or recurrent intolerance develops following dose adjustment, discontinue treatment with PegIntron.

Dose reduction is recommended if the neutrophil count is < 0.75 x 10^9/l or if the platelet count is < 50,000 x 10^9/l. Discontinuation of treatment is recommended if the neutrophil count is < 0.50 x 10^9/l or if the platelet count is < 25,000 x 10^9/l.

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Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- ***Hypersensitivity to the active substance or to any of the excipients;***
- ***Hypersensitivity to any interferon;***
- Autoimmune hepatitis or a history of autoimmune disease;
- Pre-existing severe psychiatric condition or a history of severe psychiatric disorder;
- ***Pre-existing thyroid abnormalities for which thyroid function cannot be maintained in the normal range by medication;***
- Severe renal or hepatic dysfunction;
- Epilepsy and/or compromised central nervous system (CNS) function;
- Pregnancy.

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Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

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Liver function: Discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

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*Pulmonary changes****: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. The aetiology has not been defined. These symptoms have been reported more frequently in patients treated with interferon alpha when shosaikoto, a Chinese herbal medicine, is administered concomitantly. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.***

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Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons. Any patient complaining of loss of visual acuity or visual field must have an eye examination. Because these ocular events may occur in conjunction with other disease states, a visual exam prior to initiation of PegIntron therapy is recommended in patients with diabetes mellitus or hypertension.

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No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. PegIntron should not be used during pregnancy (see **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

It is not known whether the components of this medicinal product are excreted in human milk. Therefore, a decision must be made whether to discontinue treatment or discontinue nursing, taking into account the importance of the treatment to the mother.

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

Based on a clinical database of 940 PegIntron treated patients of whom 754 received 0.5 to 1.5 microgram/kg for a year, most undesirable effects were mild or moderate in severity and not treatment limiting.

Table 1 Adverse events reported very commonly in clinical trials (≥ 10 % of patients)			
	PegIntron 0.5 microgram/kg once weekly N=315	PegIntron 1.0 microgram/kg once weekly N=297	IntronA 3 MIU three times a week N=303
Application Site Disorders			
Inflammation	44 %	42 %	16 %
Reaction	7 %	10 %	5 %
General Body Discomfort			
Asthenia	12 %	12 %	11 %
Dizziness	8 %	12 %	10 %
Fatigue	43 %	51 %	50 %
Fever	31 %	45 %	30 %
Headache	61 %	64 %	58 %
Flu-like Symptoms	18 %	22 %	19 %
Rigors	34 %	40 %	33 %
Weight Decrease	10 %	11 %	13 %
Gastro-intestinal			
Anorexia	10 %	20 %	17 %
Nausea	21 %	26 %	20 %
Diarrhoea	16 %	18 %	16 %
Abdominal Pain	14 %	15 %	11 %
Musculoskeletal			
Pain	19 %	28 %	22 %
Myalgia	48 %	54 %	53 %
Arthralgia	26 %	25 %	27 %
Psychiatric			
Depression	27 %	29 %	25 %
Anxiety	10 %	9 %	10 %
Concentration Impaired	10 %	10 %	8 %
Insomnia	17 %	23 %	23 %
Irritability	19 %	18 %	24 %
Alopecia	20 %	22 %	22 %
Pharyngitis	12 %	10 %	7 %

Commonly reported undesirable effects (≥ 2 % of patients) were pruritus, skin dry, malaise, sweating increased, right upper quadrant pain, neutropaenia, rash, vomiting, mouth dry, emotional lability, nervousness, dyspnoea, viral infection, somnolence, thyroid disorders, chest pain, dyspepsia, flushing, paresthaesia, coughing, agitation, sinusitis, hypertonia, hyperesthaesia, vision blurred, confusion, flatulence, libido decreased, erythema, eye pain, apathy, hypoesthaesia, loose stool, conjunctivitis, nasal congestion, constipation, vertigo, menorrhagia, menstrual disorder.

Rarely reported events include suicidal ideation and attempted suicide, hearing and retinal disorders, diabetes, hepatopathy and arrhythmia.

Granulocytopaenia (< 0.75 x 10^9/l) occurred in 4 and 7 % and thrombocytopaenia (< 70 x 10^9/l) in 1 and 3 % respectively of patients receiving 0.5 or 1.0 microgram/kg of PegIntron.

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators, Interferons, Peginterferon alfa-2b, ATC code: L03A B10.

PegIntron is a covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol. The average molecular weight of the molecule is approximately 31,300 daltons.

1.3.1.1. Interferon alfa-2b

Recombinant interferon alfa-2b is obtained from a clone of *E. coli*, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

In vitro and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

1.4. PegIntron

PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of Week 4 correlated with the dose of PegIntron.

1.5. PegIntron clinical trial results

The safety and efficacy of 48 weeks of treatment with 3 doses of PegIntron (0.5, 1.0, and 1.5 micrograms/kg administered subcutaneously once weekly) vs. IntronA (3 million IU administered subcutaneously 3 times a week) were studied in 1,219 treatment-naive patients with chronic hepatitis C. Table 2 provides sustained virologic response (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

Table 2 Proportion of patients with sustained loss of HCV

(%) of patients

	A	B	C	D	p Value**
Response*	PegIntron 0.5 micro-gram/kg N=315	PegIntron 1.0 micro-gram/kg N=297	PegIntron 1.5 micro-grams/kg N=304	IntronA 3 MIU N=303	*A vs D B vs D C vs D*
Sustained Response 6 Months Post	57 (18 %)	73 (25 %)	71 (23 %)	37 (12 %)	0.042 < 0.001 < 0.001

Treatment					
* Serum HCV-RNA is measured by quantitative polymerase chain reaction with a lower limit of detection of 100 copies/ml (National Genetics Institute, Culver City, CA) ** Chi-square Test					

Table 3 Sustained Virologic Response by HCV Virus Level (copies/ml) and Genotype				
	Number (%) of Subjects			
	PegIntron 0.5 µg/kg	PegIntron 1.0 µg/kg	PegIntron 1.5 µg/kg	IntronA 3 MIU
Genotype 1				
≤ 2 million	14/52 (27)	16/42 (38)	19/56 (34)	10/48 (21)
> 2 million	8/159 (5)	12/157 (8)	12/167 (7)	4/169 (2)
Genotypes 2/3				
≤ 2 million	14/24 (58)	13/21 (62)	15/22 (68)	9/25 (36)
> 2 million	17/64 (27)	26/62 (42)	21/51 (41)	14/56 (25)

In general, most side effects were dose-related, and the Quality of Life was less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of IntronA three times a week (see also **4.8**).

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.
Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean PegIntron elimination half life is approximately 30.7 hours (range 27-33 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been

fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see **4.2**).

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors**: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.**

5.3 Preclinical safety data

Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to 4 weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential.

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

Solvent for parenteral use: water for injections

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also **6.6**).

6.3 Shelf life

2 years

After reconstitution:

- ***Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.***
- ***From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.***

6.4 Special precautions for storage

Store at 2°C - 8°C

6.5 Nature and contents of container

The powder is contained in a 2 ml vial, Type I flint glass, with a butyl rubber stopper in an aluminium flip-off seal with a polypropylene bonnet. The solvent is presented in a 2 ml ampoule, Type I flint glass.

PegIntron 80 micrograms is supplied as:

- ***1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;***
- ***1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;***
- ***4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;***
- ***4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;***
- ***6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use.***

6.6 Instructions for use and handling, and disposal

PegIntron is supplied as a powder of peginterferon alfa-2b at a strength of 80 micrograms for single use. Each vial must be reconstituted with 0.7 ml of water for injections for administration of up to 0.5 ml of solution. The reconstituted solution has a concentration of 80 micrograms/0.5 ml.

Using a sterilised injection syringe and injection needle, inject 0.7 ml of water for injections into the vial of PegIntron. Agitate gently to complete dissolution of powder. The appropriate dose can then be withdrawn with a sterilised injection syringe and injected.

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. Do not use if discolouration is present. Discard any unused material.

7. MARKETING AUTHORISATION HOLDER

SP Europe

73, rue de Stalle

B-1180 Bruxelles

Belgium

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of PegIntron, powder for solution for injection contains 100 micrograms of peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol).
Each vial provides 100 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PegIntron is indicated in monotherapy in case of intolerance or contraindication to ribavirin, for the treatment of adult patients with histologically proven chronic hepatitis C who have serum markers for virus C replication, e.g. those who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV.

The optimal treatment for chronic hepatitis C is considered to be the administration of a combination of interferon alfa-2b with ribavirin.
The safety and efficacy of the combination of PegIntron and ribavirin has not yet been documented.

4.2 Posology and method of administration

PegIntron treatment should be initiated only by a physician experienced in the treatment of patients with hepatitis C.

PegIntron monotherapy is administered subcutaneously at a dose of 0.5 or 1.0 microgram/kg once weekly for at least 6 months. The dose should be selected based on the anticipated efficacy and safety (see 4.8 and 5.1). In patients showing loss of HCV-RNA at 6 months, treatment is continued for an additional 6 months, i.e.1 year of treatment.

If adverse events develop during the course of treatment, it is recommended that the dose of PegIntron be modified to one-half the starting dose once weekly. If persistent or recurrent intolerance develops following dose adjustment, discontinue treatment with PegIntron.

Dose reduction is recommended if the neutrophil count is < 0.75 x 10^9/l or if the platelet count is < 50,000 x 10^9/l. Discontinuation of treatment is recommended if the neutrophil count is < 0.50 x 10^9/l or if the platelet count is < 25,000 x 10^9/l.

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment (creatinine clearance ≤ 50 ml/minute) (see **5.2**). It is recommended that these patients be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in hepatic impairment: The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- ***Hypersensitivity to the active substance or to any of the excipients;***
- ***Hypersensitivity to any interferon;***
- Autoimmune hepatitis or a history of autoimmune disease;
- Pre-existing severe psychiatric condition or a history of severe psychiatric disorder;
- ***Pre-existing thyroid abnormalities for which thyroid function cannot be maintained in the normal range by medication;***
- Severe renal or hepatic dysfunction;
- Epilepsy and/or compromised central nervous system (CNS) function;
- Pregnancy.

4.4 Special warnings and special precautions for use

Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been rarely observed during interferon alfa-2b therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Liver function: Discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

*Debilitating medical conditions****: PegIntron must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.***

*Pulmonary changes****: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. The aetiology has not been defined. These symptoms have been reported more frequently in patients treated with interferon alpha when shosaikoto, a Chinese herbal medicine, is administered concomitantly. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt***

discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

*Autoimmune disease****: The development of auto-antibodies has been reported during treatment with alpha interferons. Clinical manifestations of autoimmune disease during interferon therapy may occur more frequently in patients predisposed to the development of autoimmune disorders.***

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons. Any patient complaining of loss of visual acuity or visual field must have an eye examination. Because these ocular events may occur in conjunction with other disease states, a visual exam prior to initiation of PegIntron therapy is recommended in patients with diabetes mellitus or hypertension.

Psychiatric and Central Nervous System (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy. Other CNS effects manifested by confusion and other alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PegIntron therapy.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alfa-2b have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using interferon alfa-2b 2.8 % patients overall developed thyroid abnormalities. These were controlled by conventional therapy for thyroid dysfunction. The mechanism by which alpha interferons may alter thyroid status is unknown. Prior to initiation of PegIntron therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. PegIntron treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

*Other****: Due to reports of interferon alfa-2b exacerbating pre-existing psoriatic disease, use of PegIntron in patients with psoriasis is recommended only if the potential benefit justifies the potential risk.***

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function are recommended in all patients prior to and periodically during treatment with PegIntron. Acceptable baseline values that may be considered as a guideline are:

- Platelets ≥ 100,000/mm^3
- Neutrophil count ≥ 1,500/mm^3
- Thyroid Stimulating Hormone (TSH) level must be within normal limits

4.5 Interaction with other medicinal products and other forms of interaction

Results of a single-dose study with PegIntron demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50 % reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. PegIntron should not be used during pregnancy (see **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

It is not known whether the components of this medicinal product are excreted in human milk. Therefore, a decision must be made whether to discontinue treatment or discontinue nursing, taking into account the importance of the treatment to the mother.

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

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Rarely reported events include suicidal ideation and attempted suicide, hearing and retinal disorders, diabetes, hepatopathy and arrhythmia.

Granulocytopaenia (< 0.75 x 10^9/l) occurred in 4 and 7 % and thrombocytopaenia (< 70 x 10^9/l) in 1 and 3 % respectively of patients receiving 0.5 or 1.0 microgram/kg of PegIntron.

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

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Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

1.6. PegIntron

PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of Week 4 correlated with the dose of PegIntron.

1.7. PegIntron clinical trial results

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Table 2 Proportion of patients with sustained loss of HCV

(%) of patients

	A	B	C	D	p Value**
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Sustained Response 6 Months Post	57 (18 %)	73 (25 %)	71 (23 %)	37 (12 %)	0.042 < 0.001 < 0.001

Treatment					

* Serum HCV-RNA is measured by quantitative polymerase chain reaction with a lower limit of detection of 100 copies/ml (National Genetics Institute, Culver City, CA)

** Chi-square Test

Table 3 Sustained Virologic Response by HCV Virus Level (copies/ml) and Genotype

	Number (%) of Subjects			
	PegIntron 0.5 µg/kg	PegIntron 1.0 µg/kg	PegIntron 1.5 µg/kg	IntronA 3 MIU
Genotype 1				
≤ 2 million	14/52 (27)	16/42 (38)	19/56 (34)	10/48 (21)
> 2 million	8/159 (5)	12/157 (8)	12/167 (7)	4/169 (2)
Genotypes 2/3				
≤ 2 million	14/24 (58)	13/21 (62)	15/22 (68)	9/25 (36)
> 2 million	17/64 (27)	26/62 (42)	21/51 (41)	14/56 (25)

In general, most side effects were dose-related, and the Quality of Life was less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of IntronA three times a week (see also **4.8**).

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.
Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean PegIntron elimination half life is approximately 30.7 hours (range 27-33 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been

fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see **4.2**).

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors**: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.**

5.3 Preclinical safety data

Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to 4 weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential.

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

Solvent for parenteral use: water for injections

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also **6.6**).

6.3 Shelf life

2 years

After reconstitution:

- ***Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.***
- ***From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.***

6.4 Special precautions for storage

Store at 2°C - 8°C

6.5 Nature and contents of container

The powder is contained in a 2 ml vial, Type I flint glass, with a butyl rubber stopper in an aluminium flip-off seal with a polypropylene bonnet. The solvent is presented in a 2 ml ampoule, Type I flint glass.

PegIntron 100 micrograms is supplied as:

- ***1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;***
- ***1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;***
- ***4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;***
- ***4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;***
- ***6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use.***

6.6 Instructions for use and handling, and disposal

PegIntron is supplied as a powder of peginterferon alfa-2b at a strength of 100 micrograms for single use. Each vial must be reconstituted with 0.7 ml of water for injections for administration of up to 0.5 ml of solution. The reconstituted solution has a concentration of 100 micrograms/0.5 ml.

Using a sterilised injection syringe and injection needle, inject 0.7 ml of water for injections into the vial of PegIntron. Agitate gently to complete dissolution of powder. The appropriate dose can then be withdrawn with a sterilised injection syringe and injected.

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. Do not use if discolouration is present. Discard any unused material.

7. MARKETING AUTHORISATION HOLDER

SP Europe

73, rue de Stalle

B-1180 Bruxelles

Belgium

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of PegIntron, powder for solution for injection contains 120 micrograms of peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol).
Each vial provides 120 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PegIntron is indicated in monotherapy in case of intolerance or contraindication to ribavirin, for the treatment of adult patients with histologically proven chronic hepatitis C who have serum markers for virus C replication, e.g. those who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV.

The optimal treatment for chronic hepatitis C is considered to be the administration of a combination of interferon alfa-2b with ribavirin.
The safety and efficacy of the combination of PegIntron and ribavirin has not yet been documented.

4.2 Posology and method of administration

PegIntron treatment should be initiated only by a physician experienced in the treatment of patients with hepatitis C.

PegIntron monotherapy is administered subcutaneously at a dose of 0.5 or 1.0 microgram/kg once weekly for at least 6 months. The dose should be selected based on the anticipated efficacy and safety (see 4.8 and 5.1). In patients showing loss of HCV-RNA at 6 months, treatment is continued for an additional 6 months, i.e.1 year of treatment.

If adverse events develop during the course of treatment, it is recommended that the dose of PegIntron be modified to one-half the starting dose once weekly. If persistent or recurrent intolerance develops following dose adjustment, discontinue treatment with PegIntron.

Dose reduction is recommended if the neutrophil count is < 0.75 x 10^9/l or if the platelet count is < 50,000 x 10^9/l. Discontinuation of treatment is recommended if the neutrophil count is < 0.50 x 10^9/l or if the platelet count is < 25,000 x 10^9/l.

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment (creatinine clearance ≤ 50 ml/minute) (see **5.2**). It is recommended that these patients be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in hepatic impairment: The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- ***Hypersensitivity to the active substance or to any of the excipients;***
- ***Hypersensitivity to any interferon;***
- Autoimmune hepatitis or a history of autoimmune disease;
- Pre-existing severe psychiatric condition or a history of severe psychiatric disorder;
- ***Pre-existing thyroid abnormalities for which thyroid function cannot be maintained in the normal range by medication;***
- Severe renal or hepatic dysfunction;
- Epilepsy and/or compromised central nervous system (CNS) function;
- Pregnancy.

4.4 Special warnings and special precautions for use

Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been rarely observed during interferon alfa-2b therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Liver function: Discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

*Debilitating medical conditions****: PegIntron must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.***

*Pulmonary changes****: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. The aetiology has not been defined. These symptoms have been reported more frequently in patients treated with interferon alpha when shosaikoto, a Chinese herbal medicine, is administered concomitantly. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt***

discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

*Autoimmune disease****: The development of auto-antibodies has been reported during treatment with alpha interferons. Clinical manifestations of autoimmune disease during interferon therapy may occur more frequently in patients predisposed to the development of autoimmune disorders.***

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons. Any patient complaining of loss of visual acuity or visual field must have an eye examination. Because these ocular events may occur in conjunction with other disease states, a visual exam prior to initiation of PegIntron therapy is recommended in patients with diabetes mellitus or hypertension.

Psychiatric and Central Nervous System (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy. Other CNS effects manifested by confusion and other alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PegIntron therapy.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alfa-2b have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using interferon alfa-2b 2.8 % patients overall developed thyroid abnormalities. These were controlled by conventional therapy for thyroid dysfunction. The mechanism by which alpha interferons may alter thyroid status is unknown. Prior to initiation of PegIntron therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. PegIntron treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

*Other****: Due to reports of interferon alfa-2b exacerbating pre-existing psoriatic disease, use of PegIntron in patients with psoriasis is recommended only if the potential benefit justifies the potential risk.***

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function are recommended in all patients prior to and periodically during treatment with PegIntron. Acceptable baseline values that may be considered as a guideline are:

- Platelets ≥ 100,000/mm^3
- Neutrophil count ≥ 1,500/mm^3
- Thyroid Stimulating Hormone (TSH) level must be within normal limits

4.5 Interaction with other medicinal products and other forms of interaction

Results of a single-dose study with PegIntron demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50 % reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. PegIntron should not be used during pregnancy (see **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

It is not known whether the components of this medicinal product are excreted in human milk. Therefore, a decision must be made whether to discontinue treatment or discontinue nursing, taking into account the importance of the treatment to the mother.

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

Based on a clinical database of 940 PegIntron treated patients of whom 754 received 0.5 to 1.5 microgram/kg for a year, most undesirable effects were mild or moderate in severity and not treatment limiting.

Table 1 Adverse events reported very commonly in clinical trials (≥ 10 % of patients)			
	PegIntron 0.5 microgram/kg once weekly N=315	PegIntron 1.0 microgram/kg once weekly N=297	IntronA 3 MIU three times a week N=303
Application Site Disorders			
Inflammation	44 %	42 %	16 %
Reaction	7 %	10 %	5 %
General Body Discomfort			
Asthenia	12 %	12 %	11 %
Dizziness	8 %	12 %	10 %
Fatigue	43 %	51 %	50 %
Fever	31 %	45 %	30 %
Headache	61 %	64 %	58 %
Flu-like Symptoms	18 %	22 %	19 %
Rigors	34 %	40 %	33 %
Weight Decrease	10 %	11 %	13 %
Gastro-intestinal			
Anorexia	10 %	20 %	17 %
Nausea	21 %	26 %	20 %
Diarrhoea	16 %	18 %	16 %
Abdominal Pain	14 %	15 %	11 %
Musculoskeletal			
Pain	19 %	28 %	22 %
Myalgia	48 %	54 %	53 %
Arthralgia	26 %	25 %	27 %
Psychiatric			
Depression	27 %	29 %	25 %
Anxiety	10 %	9 %	10 %
Concentration Impaired	10 %	10 %	8 %
Insomnia	17 %	23 %	23 %
Irritability	19 %	18 %	24 %
Alopecia	20 %	22 %	22 %
Pharyngitis	12 %	10 %	7 %

Commonly reported undesirable effects (≥ 2 % of patients) were pruritus, skin dry, malaise, sweating increased, right upper quadrant pain, neutropaenia, rash, vomiting, mouth dry, emotional lability, nervousness, dyspnoea, viral infection, somnolence, thyroid disorders, chest pain, dyspepsia, flushing, paresthaesia, coughing, agitation, sinusitis, hypertonia, hyperesthaesia, vision blurred, confusion, flatulence, libido decreased, erythema, eye pain, apathy, hypoesthaesia, loose stool, conjunctivitis, nasal congestion, constipation, vertigo, menorrhagia, menstrual disorder.

Rarely reported events include suicidal ideation and attempted suicide, hearing and retinal disorders, diabetes, hepatopathy and arrhythmia.

Granulocytopaenia (< 0.75 x 10^9/l) occurred in 4 and 7 % and thrombocytopaenia (< 70 x 10^9/l) in 1 and 3 % respectively of patients receiving 0.5 or 1.0 microgram/kg of PegIntron.

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators, Interferons, Peginterferon alfa-2b, ATC code: L03A B10.

PegIntron is a covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol. The average molecular weight of the molecule is approximately 31,300 daltons.

1.7.1.1. Interferon alfa-2b

Recombinant interferon alfa-2b is obtained from a clone of *E. coli*, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

In vitro and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

1.8. PegIntron

PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of Week 4 correlated with the dose of PegIntron.

1.9. PegIntron clinical trial results

The safety and efficacy of 48 weeks of treatment with 3 doses of PegIntron (0.5, 1.0, and 1.5 micrograms/kg administered subcutaneously once weekly) vs. IntronA (3 million IU administered subcutaneously 3 times a week) were studied in 1,219 treatment-naive patients with chronic hepatitis C. Table 2 provides sustained virologic response (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

Table 2 Proportion of patients with sustained loss of HCV

(%) of patients

	A	B	C	D	p Value**
Response*	PegIntron 0.5 micro-gram/kg N=315	PegIntron 1.0 micro-gram/kg N=297	PegIntron 1.5 micro-grams/kg N=304	IntronA 3 MIU N=303	*A vs D B vs D C vs D*
Sustained Response 6 Months Post	57 (18 %)	73 (25 %)	71 (23 %)	37 (12 %)	0.042 < 0.001 < 0.001

Treatment					
* Serum HCV-RNA is measured by quantitative polymerase chain reaction with a lower limit of detection of 100 copies/ml (National Genetics Institute, Culver City, CA) ** Chi-square Test					

Table 3 Sustained Virologic Response by HCV Virus Level (copies/ml) and Genotype

	Number (%) of Subjects			
	PegIntron 0.5 µg/kg	PegIntron 1.0 µg/kg	PegIntron 1.5 µg/kg	IntronA 3 MIU
Genotype 1				
≤ 2 million	14/52 (27)	16/42 (38)	19/56 (34)	10/48 (21)
> 2 million	8/159 (5)	12/157 (8)	12/167 (7)	4/169 (2)
Genotypes 2/3				
≤ 2 million	14/24 (58)	13/21 (62)	15/22 (68)	9/25 (36)
> 2 million	17/64 (27)	26/62 (42)	21/51 (41)	14/56 (25)

In general, most side effects were dose-related, and the Quality of Life was less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of IntronA three times a week (see also **4.8**).

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.
Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean PegIntron elimination half life is approximately 30.7 hours (range 27-33 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been

fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see **4.2**).

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors**: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.**

5.3 Preclinical safety data

Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to 4 weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential.

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

Solvent for parenteral use: water for injections

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also **6.6**).

6.3 Shelf life

2 years

After reconstitution:

- ***Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.***
- ***From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.***

6.4 Special precautions for storage

Store at 2°C - 8°C

6.5 Nature and contents of container

The powder is contained in a 2 ml vial, Type I flint glass, with a butyl rubber stopper in an aluminium flip-off seal with a polypropylene bonnet. The solvent is presented in a 2 ml ampoule, Type I flint glass.

PegIntron 120 micrograms is supplied as:

- ***1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;***
- ***1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;***
- ***4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;***
- ***4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;***
- ***6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use.***

6.6 Instructions for use and handling, and disposal

PegIntron is supplied as a powder of peginterferon alfa-2b at a strength of 120 micrograms for single use. Each vial must be reconstituted with 0.7 ml of water for injections for administration of up to 0.5 ml of solution. The reconstituted solution has a concentration of 120 micrograms/0.5 ml.

Using a sterilised injection syringe and injection needle, inject 0.7 ml of water for injections into the vial of PegIntron. Agitate gently to complete dissolution of powder. The appropriate dose can then be withdrawn with a sterilised injection syringe and injected.

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. Do not use if discolouration is present. Discard any unused material.

7. MARKETING AUTHORISATION HOLDER

SP Europe

73, rue de Stalle

B-1180 Bruxelles

Belgium

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of PegIntron, powder for solution for injection contains 150 micrograms of peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol).
Each vial provides 150 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PegIntron is indicated in monotherapy in case of intolerance or contraindication to ribavirin, for the treatment of adult patients with histologically proven chronic hepatitis C who have serum markers for virus C replication, e.g. those who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV.

The optimal treatment for chronic hepatitis C is considered to be the administration of a combination of interferon alfa-2b with ribavirin.
The safety and efficacy of the combination of PegIntron and ribavirin has not yet been documented.

4.2 Posology and method of administration

PegIntron treatment should be initiated only by a physician experienced in the treatment of patients with hepatitis C.

PegIntron monotherapy is administered subcutaneously at a dose of 0.5 or 1.0 microgram/kg once weekly for at least 6 months. The dose should be selected based on the anticipated efficacy and safety (see 4.8 and 5.1). In patients showing loss of HCV-RNA at 6 months, treatment is continued for an additional 6 months, i.e.1 year of treatment.

If adverse events develop during the course of treatment, it is recommended that the dose of PegIntron be modified to one-half the starting dose once weekly. If persistent or recurrent intolerance develops following dose adjustment, discontinue treatment with PegIntron.

Dose reduction is recommended if the neutrophil count is < 0.75 x 10^9/l or if the platelet count is < 50,000 x 10^9/l. Discontinuation of treatment is recommended if the neutrophil count is < 0.50 x 10^9/l or if the platelet count is < 25,000 x 10^9/l.

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment (creatinine clearance ≤ 50 ml/minute) (see **5.2**). It is recommended that these patients be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in hepatic impairment: The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- ***Hypersensitivity to the active substance or to any of the excipients;***
- ***Hypersensitivity to any interferon;***
- Autoimmune hepatitis or a history of autoimmune disease;
- Pre-existing severe psychiatric condition or a history of severe psychiatric disorder;
- ***Pre-existing thyroid abnormalities for which thyroid function cannot be maintained in the normal range by medication;***
- Severe renal or hepatic dysfunction;
- Epilepsy and/or compromised central nervous system (CNS) function;
- Pregnancy.

4.4 Special warnings and special precautions for use

Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been rarely observed during interferon alfa-2b therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Liver function: Discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

*Debilitating medical conditions****: PegIntron must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.***

*Pulmonary changes****: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. The aetiology has not been defined. These symptoms have been reported more frequently in patients treated with interferon alpha when shosaikoto, a Chinese herbal medicine, is administered concomitantly. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt***

discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

*Autoimmune disease****: The development of auto-antibodies has been reported during treatment with alpha interferons. Clinical manifestations of autoimmune disease during interferon therapy may occur more frequently in patients predisposed to the development of autoimmune disorders.***

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons. Any patient complaining of loss of visual acuity or visual field must have an eye examination. Because these ocular events may occur in conjunction with other disease states, a visual exam prior to initiation of PegIntron therapy is recommended in patients with diabetes mellitus or hypertension.

Psychiatric and Central Nervous System (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy. Other CNS effects manifested by confusion and other alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PegIntron therapy.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alfa-2b have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using interferon alfa-2b 2.8 % patients overall developed thyroid abnormalities. These were controlled by conventional therapy for thyroid dysfunction. The mechanism by which alpha interferons may alter thyroid status is unknown. Prior to initiation of PegIntron therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. PegIntron treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

*Other****: Due to reports of interferon alfa-2b exacerbating pre-existing psoriatic disease, use of PegIntron in patients with psoriasis is recommended only if the potential benefit justifies the potential risk.***

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function are recommended in all patients prior to and periodically during treatment with PegIntron. Acceptable baseline values that may be considered as a guideline are:

- Platelets ≥ 100,000/mm^3
- Neutrophil count ≥ 1,500/mm^3
- Thyroid Stimulating Hormone (TSH) level must be within normal limits

4.5 Interaction with other medicinal products and other forms of interaction

Results of a single-dose study with PegIntron demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50 % reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. PegIntron should not be used during pregnancy (see **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

It is not known whether the components of this medicinal product are excreted in human milk. Therefore, a decision must be made whether to discontinue treatment or discontinue nursing, taking into account the importance of the treatment to the mother.

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

Based on a clinical database of 940 PegIntron treated patients of whom 754 received 0.5 to 1.5 microgram/kg for a year, most undesirable effects were mild or moderate in severity and not treatment limiting.

Table 1 Adverse events reported very commonly in clinical trials (≥ 10 % of patients)			
	PegIntron 0.5 microgram/kg once weekly N=315	PegIntron 1.0 microgram/kg once weekly N=297	IntronA 3 MIU three times a week N=303
Application Site Disorders			
Inflammation	44 %	42 %	16 %
Reaction	7 %	10 %	5 %
General Body Discomfort			
Asthenia	12 %	12 %	11 %
Dizziness	8 %	12 %	10 %
Fatigue	43 %	51 %	50 %
Fever	31 %	45 %	30 %
Headache	61 %	64 %	58 %
Flu-like Symptoms	18 %	22 %	19 %
Rigors	34 %	40 %	33 %
Weight Decrease	10 %	11 %	13 %
Gastro-intestinal			
Anorexia	10 %	20 %	17 %
Nausea	21 %	26 %	20 %
Diarrhoea	16 %	18 %	16 %
Abdominal Pain	14 %	15 %	11 %
Musculoskeletal			
Pain	19 %	28 %	22 %
Myalgia	48 %	54 %	53 %
Arthralgia	26 %	25 %	27 %
Psychiatric			
Depression	27 %	29 %	25 %
Anxiety	10 %	9 %	10 %
Concentration Impaired	10 %	10 %	8 %
Insomnia	17 %	23 %	23 %
Irritability	19 %	18 %	24 %
Alopecia	20 %	22 %	22 %
Pharyngitis	12 %	10 %	7 %

Commonly reported undesirable effects (≥ 2 % of patients) were pruritus, skin dry, malaise, sweating increased, right upper quadrant pain, neutropaenia, rash, vomiting, mouth dry, emotional lability, nervousness, dyspnoea, viral infection, somnolence, thyroid disorders, chest pain, dyspepsia, flushing, paresthaesia, coughing, agitation, sinusitis, hypertonia, hyperesthaesia, vision blurred, confusion, flatulence, libido decreased, erythema, eye pain, apathy, hypoesthaesia, loose stool, conjunctivitis, nasal congestion, constipation, vertigo, menorrhagia, menstrual disorder.

Rarely reported events include suicidal ideation and attempted suicide, hearing and retinal disorders, diabetes, hepatopathy and arrhythmia.

Granulocytopaenia (< 0.75 x 10^9/l) occurred in 4 and 7 % and thrombocytopaenia (< 70 x 10^9/l) in 1 and 3 % respectively of patients receiving 0.5 or 1.0 microgram/kg of PegIntron.

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators, Interferons, Peginterferon alfa-2b, ATC code: L03A B10.

PegIntron is a covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol. The average molecular weight of the molecule is approximately 31,300 daltons.

1.9.1.1. Interferon alfa-2b

Recombinant interferon alfa-2b is obtained from a clone of *E. coli*, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

In vitro and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

1.10. PegIntron

PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of Week 4 correlated with the dose of PegIntron.

1.11. PegIntron clinical trial results

The safety and efficacy of 48 weeks of treatment with 3 doses of PegIntron (0.5, 1.0, and 1.5 micrograms/kg administered subcutaneously once weekly) vs. IntronA (3 million IU administered subcutaneously 3 times a week) were studied in 1,219 treatment-naive patients with chronic hepatitis C. Table 2 provides sustained virologic response (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

Table 2 Proportion of patients with sustained loss of HCV

(%) of patients

	A	B	C	D	p Value**
Response*	PegIntron 0.5 micro-gram/kg N=315	PegIntron 1.0 micro-gram/kg N=297	PegIntron 1.5 micro-grams/kg N=304	IntronA 3 MIU N=303	*A vs D B vs D C vs D*
Sustained Response 6 Months Post	57 (18 %)	73 (25 %)	71 (23 %)	37 (12 %)	0.042 < 0.001 < 0.001

Treatment					
* Serum HCV-RNA is measured by quantitative polymerase chain reaction with a lower limit of detection of 100 copies/ml (National Genetics Institute, Culver City, CA) ** Chi-square Test					

Table 3 Sustained Virologic Response by HCV Virus Level (copies/ml) and Genotype

	Number (%) of Subjects			
	PegIntron 0.5 µg/kg	PegIntron 1.0 µg/kg	PegIntron 1.5 µg/kg	IntronA 3 MIU
Genotype 1				
≤ 2 million	14/52 (27)	16/42 (38)	19/56 (34)	10/48 (21)
> 2 million	8/159 (5)	12/157 (8)	12/167 (7)	4/169 (2)
Genotypes 2/3				
≤ 2 million	14/24 (58)	13/21 (62)	15/22 (68)	9/25 (36)
> 2 million	17/64 (27)	26/62 (42)	21/51 (41)	14/56 (25)

In general, most side effects were dose-related, and the Quality of Life was less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of IntronA three times a week (see also **4.8**).

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.
Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean PegIntron elimination half life is approximately 30.7 hours (range 27-33 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been

fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see **4.2**).

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors**: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.**

5.3 Preclinical safety data

Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to 4 weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential.

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

Solvent for parenteral use: water for injections

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also **6.6**).

6.3 Shelf life

2 years

After reconstitution:

- ***Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.***
- ***From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.***

6.4 Special precautions for storage

Store at 2°C - 8°C

6.5 Nature and contents of container

The powder is contained in a 2 ml vial, Type I flint glass, with a butyl rubber stopper in an aluminium flip-off seal with a polypropylene bonnet. The solvent is presented in a 2 ml ampoule, Type I flint glass.

PegIntron 150 micrograms is supplied as:

- ***1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;***
- ***1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;***
- ***4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;***
- ***4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;***
- ***6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use.***

6.6 Instructions for use and handling, and disposal

PegIntron is supplied as a powder of peginterferon alfa-2b at a strength of 150 micrograms for single use. Each vial must be reconstituted with 0.7 ml of water for injections for administration of up to 0.5 ml of solution. The reconstituted solution has a concentration of 150 micrograms/0.5 ml.

Using a sterilised injection syringe and injection needle, inject 0.7 ml of water for injections into the vial of PegIntron. Agitate gently to complete dissolution of powder. The appropriate dose can then be withdrawn with a sterilised injection syringe and injected.

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. Do not use if discolouration is present. Discard any unused material.

7. MARKETING AUTHORISATION HOLDER

SP Europe

73, rue de Stalle

B-1180 Bruxelles

Belgium

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE AND MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE AND MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE

Name and address of the manufacturer of the biological active substance

SP (Brinny) Company

Innishannon - County Cork

Ireland

Manufacturing Authorisation issued on 28 September 1998 by the Irish Medicines Board, Earlsfort Centre, Earlsfort Terrace, Dublin 2.

Name and address of the manufacturer responsible for batch release

SP (Brinny) Company

Innishannon - County Cork

Ireland

Manufacturing Authorisation issued on 28 September 1998 by the Irish Medicines Board, Earlsfort Centre, Earlsfort Terrace, Dublin 2.

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 4.2).

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 50 micrograms - 1 vial of powder, 1 ampoule of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 50 micrograms of peginterferon alfa-2b and provides 50 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
50 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 50 micrograms - 1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles, 1 cleansing swab

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 50 micrograms of peginterferon alfa-2b and provides 50 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
50 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

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Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 50 micrograms - 4 vials of powder, 4 ampoules of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 50 micrograms of peginterferon alfa-2b and provides 50 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

4 vials of powder, 4 ampoules of solvent
50 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 50 micrograms - 4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles, 4 cleansing swabs

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 50 micrograms of peginterferon alfa-2b and provides 50 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
50 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 50 micrograms - 6 vials of powder, 6 ampoules of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 50 micrograms of peginterferon alfa-2b and provides 50 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

6 vials of powder, 6 ampoules of solvent
50 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 50 micrograms

Immediate packaging (label) - vial of powder

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

PegIntron 50 micrograms powder for injection

S.C.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

Exp

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 micrograms/0.5 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 80 micrograms - 1 vial of powder, 1 ampoule of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 80 micrograms of peginterferon alfa-2b and provides 80 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
80 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 80 micrograms - 1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles, 1 cleansing swab

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 80 micrograms of peginterferon alfa-2b and provides 80 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
80 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 80 micrograms - 4 vials of powder, 4 ampoules of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 80 micrograms of peginterferon alfa-2b and provides 80 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

4 vials of powder, 4 ampoules of solvent
80 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 80 micrograms - 4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles, 4 cleansing swabs

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 80 micrograms of peginterferon alfa-2b and provides 80 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
80 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 80 micrograms - 6 vials of powder, 6 ampoules of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 80 micrograms of peginterferon alfa-2b and provides 80 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

6 vials of powder, 6 ampoules of solvent
80 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2℃ - 8℃ (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 80 micrograms

Immediate packaging (label) - vial of powder

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

PegIntron 80 micrograms powder for injection

S.C.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

Exp

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

80 micrograms/0.5 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 100 micrograms - 1 vial of powder, 1 ampoule of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 100 micrograms of peginterferon alfa-2b and provides 100 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
100 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 100 micrograms - 1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles, 1 cleansing swab

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 100 micrograms of peginterferon alfa-2b and provides 100 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
100 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 100 micrograms - 4 vials of powder, 4 ampoules of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 100 micrograms of peginterferon alfa-2b and provides 100 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

4 vials of powder, 4 ampoules of solvent
100 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 100 micrograms - 4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles, 4 cleansing swabs

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 100 micrograms of peginterferon alfa-2b and provides 100 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
100 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 100 micrograms - 6 vials of powder, 6 ampoules of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 100 micrograms of peginterferon alfa-2b and provides 100 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

6 vials of powder, 6 ampoules of solvent
100 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2℃ - 8℃ (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 100 micrograms

Immediate packaging (label) - vial of powder

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

PegIntron 100 micrograms powder for injection

S.C.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

Exp

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 micrograms/0.5 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 120 micrograms - 1 vial of powder, 1 ampoule of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 120 micrograms of peginterferon alfa-2b and provides 120 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
120 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 120 micrograms - 1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles, 1 cleansing swab

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 120 micrograms of peginterferon alfa-2b and provides 120 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
120 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 120 micrograms - 4 vials of powder, 4 ampoules of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 120 micrograms of peginterferon alfa-2b and provides 120 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

4 vials of powder, 4 ampoules of solvent
120 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 120 micrograms - 4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles, 4 cleansing swabs

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 120 micrograms of peginterferon alfa-2b and provides 120 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
120 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 120 micrograms - 6 vials of powder, 6 ampoules of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 120 micrograms of peginterferon alfa-2b and provides 120 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

6 vials of powder, 6 ampoules of solvent
120 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2℃ - 8℃ (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 120 micrograms

Immediate packaging (label) - vial of powder

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

PegIntron 120 micrograms powder for injection

S.C.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

Exp

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 micrograms/0.5 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 150 micrograms - 1 vial of powder, 1 ampoule of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 150 micrograms of peginterferon alfa-2b and provides 150 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
150 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 150 micrograms - 1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles, 1 cleansing swab

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 150 micrograms of peginterferon alfa-2b and provides 150 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
150 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 150 micrograms - 4 vials of powder, 4 ampoules of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 150 micrograms of peginterferon alfa-2b and provides 150 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

4 vials of powder, 4 ampoules of solvent
150 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 150 micrograms - 4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles, 4 cleansing swabs

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 150 micrograms of peginterferon alfa-2b and provides 150 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
150 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 150 micrograms - 6 vials of powder, 6 ampoules of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms powder and solvent for solution for injection

peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 150 micrograms of peginterferon alfa-2b and provides 150 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

6 vials of powder, 6 ampoules of solvent
150 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2℃ - 8℃ (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 150 micrograms

Immediate packaging (label) - vial of powder

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

PegIntron 150 micrograms powder for injection

S.C.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

Exp

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

150 micrograms/0.5 ml

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron

Immediate packaging (label) - ampoule of solvent

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

Solvent for PegIntron

Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

Exp

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.7 ml

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

[Name of the medicinal product]

PegIntron 50 micrograms powder and solvent for solution for injection

peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol)

[Full statement of the active substance(s) and excipient(s)]

- The active substance is peginterferon alfa-2b, 50 micrograms/0.5 ml.
- The other ingredients are:
  Powder: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80;
  Solvent: water for injections 0.7 ml/ampoule.

[Name and address of the marketing authorisation holder and of the manufacturing authorisation holder responsible for batch release, if different]

Marketing Authorisation Holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

Manufacturer: SP (Brinny) Company, Innishannon, County Cork, Ireland

1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

[Pharmaceutical form and contents; pharmacotherapeutic group]

The pharmaceutical form is: powder and solvent for solution for injection.
The powder is contained in a 2 ml vial and the solvent is presented in a 2 ml ampoule.

Therapeutic indications

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used alone, in case of intolerance or contraindication to ribavirin to treat chronic hepatitis C, a viral infection of the liver.

The optimal treatment for chronic hepatitis C is the combination of interferon alfa-2b with ribavirin.

2. BEFORE YOU USE PEGINTRON

[List of information necessary before taking the medicinal product]

PegIntron is not recommended for use in patients under the age of 18 years.

[Contraindications]

Do not use PegIntron:

- If you are hypersensitive (allergic) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are hypersensitive (allergic) to any interferon.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have had a severe nervous or mental disorder.
- If you have thyroid disease that is not well controlled with medicines.
- If you have advanced, uncontrolled liver disease (other than hepatitis C).

- If you have severe kidney disease.
- If you have a condition that causes convulsions (seizures, or “fits”).
- If you are pregnant.

[Appropriate precautions for use; special warnings]

Take special care with PegIntron:

- If you ever had a heart attack or a heart problem.
- If you have had a problem with your liver (other than hepatitis C).
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- Be sure to tell your doctor if you are taking the Chinese herbal medication shosaikoto.

[[Use by pregnant or breast-feeding women]

Pregnancy

Ask your doctor or pharmacist for advice before taking any medicine. Do not use PegIntron during pregnancy. The effect on human pregnancy is not known.

Breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron.

[Effects on the ability to drive or to use machines]

Driving and using machines:

Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

[Interaction with other medicinal products]

Using other medicines:

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

3. HOW TO USE PEGINTRON

[Instructions for proper use]

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

[Dosage]

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

PegIntron is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year.

If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

[Method and/or route(s) of administration]

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to self-inject PegIntron at the end of the package leaflet).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if discolouration of the reconstituted solution is present. Discard any solution that is left in the vial after you give yourself the injection.

[Frequency of administration]

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

[Duration of treatment]

Use PegIntron exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take it for as long as prescribed.

[Symptoms in case of overdose and actions to be taken]

If you use more PegIntron than you should:

Tell your doctor or healthcare professional as soon as possible.

[Actions to be taken when one or more doses have been missed]

If you forget to take PegIntron:

Take the dose as soon as you remember, then continue your treatment as usual.

Do not take a double dose to make up for forgotten individual doses. Contact your doctor or pharmacist if needed.

4. POSSIBLE SIDE EFFECTS

[Description of side effects]

Like all medicines, PegIntron can have side effects. Although not all of these side effects may occur, they may need medical attention if they do.

The most common side effects are irritation or redness at the site of injection, weakness, dizziness or vertigo, tired feeling, fever, headache, flu-like symptoms, shaking chills, loss of weight, loss of appetite, nausea, diarrhoea or loose stools, stomach pain, muscle aches, pain in joints and muscles, feeling depressed, feeling anxious or nervous, difficulty concentrating, trouble falling asleep or staying asleep, irritability, hair loss, and sore throat.

Other common side effects that may occur are itching, dry skin, nervousness, feeling unwell, increased sweating, pain on the right side around your ribs, rash, vomiting, dry mouth, mood swings, breathing problems, virus infection, feeling sleepy, low thyroid gland activity (which may make you feel tired), chest pain, stomach upset, flushing, numbness or tingling feeling, coughing, agitation, sinusitis, tense muscles, increased or decreased sensitivity to touch, blurred vision, confusion, intestinal gas (flatus), loss of interest in sex, redness of skin, eye pain or infection, lack of interest in life, stuffy nose, constipation, difficult menstrual period.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems, confusion; feeling depressed, numbness or tingling feeling; trouble sleeping, thinking or concentrating; severe stomach pain; fever or chills beginning after a few weeks of treatment, pain in your lower back or side; problems with your eyesight or hearing; severe bleeding from your nose [your doctor will test your blood to ensure that your white blood cell (cells that fight infection) count and platelets (blood clotting cells) are at acceptable levels].

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING PEGINTRON

[Storage conditions and expiry date]

Keep out of the reach and sight of children

Store at 2°C - 8°C (in a refrigerator)

Do not use after the expiry date stated on the carton.

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored at 2°C - 8°C (in a refrigerator).

[Where appropriate, warning against certain visible signs of deterioration]

Do not use PegIntron if you notice discolouration of the powder.

This leaflet was last approved on

Further information

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien

73, rue de Stalle/Stallestraat 73

B-1180 Bruxelles/Brussel

Tél/Tel: + 32-(0)2 370 92 11

Luxembourg/Luxemburg

Rue de Stalle 73
B-1180 Bruxelles
Belgique/Belgien

Tél: + 32-(0)2 370 92 11

Danmark

Hvedemarken 12

DK-3520 Farum

Tlf: + 45-44 95 50 66

Nederland

Maarssenbroeksedijk 4

NL-3606 AN Maarssen

Tel: + 31-(0)30 240 88 88

Deutschland

Thomas-Dehler-Straße 27

D-81737 München

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Österreich

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1.11.1.1.Ελλάδα

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Shire Park

Welwyn Garden City

Hertfordshire AL7 1TW - UK

Tel: + 44-(0)1 707 363 636

1.11.2. HOW TO SELF-INJECT PEGINTRON?

The following instructions explain how to inject PegIntron yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject PegIntron. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

1.12. Preparation

Collect necessary items before you begin:

- a vial of PegIntron powder for injection;
- an ampoule of solvent for PegIntron (water for injections);
- a 1 ml syringe;
- a long needle (for example 0.8 × 40 mm [21 gauge 1.5 inch]) to be used to add water for injections to the PegIntron powder vial;
- a short needle (for example 0.3 × 13 mm [30 gauge 0.5 inch]) for the subcutaneous injection;
- a cleansing swab.

Wash your hands carefully.

1.13. Reconstituting PegIntron powder for injection

Remove the protective cap from the PegIntron vial. Clean the rubber top of the vial with a cleansing swab. You can save the swab to clean the skin area where you will inject the dose. Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the long needle and place it firmly on to the tip of the syringe. Remove the needle guard without touching the needle and keep the syringe with the needle in your hand. Tap the top of the ampoule of solvent gently to make sure that all the liquid is at the bottom of the ampoule. Break off the top of the ampoule of solvent. Insert the needle in the ampoule of solvent and withdraw the total amount of solvent.

To prepare the PegIntron solution, insert the needle through the rubber top of the PegIntron vial and gently place the needle tip against the glass wall of the vial without touching the cleaned top of the vial with your hands.

Slowly inject the diluent, aiming the stream of liquid at the glass wall of the vial in order to avoid production of air bubbles. Do not aim the stream at the white powder at the bottom of the vial.

To dissolve the white contents, swirl the PegIntron vial with a gentle rotary motion leaving the syringe needle in the vial, until the contents are completely dissolved. **Do not shake**. If air bubbles do form, wait until the solution has settled and all bubbles have risen to the top of the solution and disappeared before withdrawing your dose from the vial. Use this solution immediately.

1.14. Measuring the dose of PegIntron from the reconstituted powder for injection

Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the PegIntron reconstituted solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw just more than the dose prescribed by your doctor into the syringe. Hold the syringe with the needle in the vial pointing up, remove the syringe from the long needle leaving the needle in the vial and without touching the tip of the syringe. Take the short needle and place it firmly on to the tip of the syringe. Remove the needle guard from the syringe needle and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing upwards, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Inspect visually the reconstituted solution prior to administration: do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

2.

2.1. Injecting the solution

Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.

Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand, hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of 45° to 90°. After the needle is in, remove the hand used to pinch the skin and use it to hold the syringe barrel. Pull back the plunger very slightly with one hand. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject into this site; withdraw the needle and repeat the procedure. Inject the solution by pushing the plunger all the way down gently.

Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.

The vial, ampoule and injection materials intended for single use must be discarded. Dispose of the syringe and needles safely in a closed container.

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

[Name of the medicinal product]

PegIntron 80 micrograms powder and solvent for solution for injection

peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol)

[Full statement of the active substance(s) and excipient(s)]

- The active substance is peginterferon alfa-2b, 80 micrograms/0.5 ml.
- The other ingredients are:
  Powder: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80;
  Solvent: water for injections 0.7 ml/ampoule.

[Name and address of the marketing authorisation holder and of the manufacturing authorisation holder responsible for batch release, if different]

Marketing Authorisation Holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

Manufacturer: SP (Brinny) Company, Innishannon, County Cork, Ireland

1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

[Pharmaceutical form and contents; pharmacotherapeutic group]

The pharmaceutical form is: powder and solvent for solution for injection.
The powder is contained in a 2 ml vial and the solvent is presented in a 2 ml ampoule.

Therapeutic indications

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used alone, in case of intolerance or contraindication to ribavirin to treat chronic hepatitis C, a viral infection of the liver.

The optimal treatment for chronic hepatitis C is the combination of interferon alfa-2b with ribavirin.

2. BEFORE YOU USE PEGINTRON

[List of information necessary before taking the medicinal product]

PegIntron is not recommended for use in patients under the age of 18 years.

[Contraindications]

Do not use PegIntron:

- If you are hypersensitive (allergic) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are hypersensitive (allergic) to any interferon.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have had a severe nervous or mental disorder.
- If you have thyroid disease that is not well controlled with medicines.
- If you have advanced, uncontrolled liver disease (other than hepatitis C).

- If you have severe kidney disease.
- If you have a condition that causes convulsions (seizures, or “fits”).
- If you are pregnant.

[Appropriate precautions for use; special warnings]

Take special care with PegIntron:

- If you ever had a heart attack or a heart problem.
- If you have had a problem with your liver (other than hepatitis C).
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- Be sure to tell your doctor if you are taking the Chinese herbal medication shosaikoto.

[[Use by pregnant or breast-feeding women]

Pregnancy

Ask your doctor or pharmacist for advice before taking any medicine. Do not use PegIntron during pregnancy. The effect on human pregnancy is not known.

Breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron.

[Effects on the ability to drive or to use machines]

Driving and using machines:

Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

[Interaction with other medicinal products]

Using other medicines:

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

3. HOW TO USE PEGINTRON

[Instructions for proper use]

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

[Dosage]

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

PegIntron is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year.

If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

[Method and/or route(s) of administration]

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to self-inject PegIntron at the end of the package leaflet).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if discolouration of the reconstituted solution is present. Discard any solution that is left in the vial after you give yourself the injection.

[Frequency of administration]

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

[Duration of treatment]

Use PegIntron exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take it for as long as prescribed.

[Symptoms in case of overdose and actions to be taken]

If you use more PegIntron than you should:

Tell your doctor or healthcare professional as soon as possible.

[Actions to be taken when one or more doses have been missed]

If you forget to take PegIntron:

Take the dose as soon as you remember, then continue your treatment as usual.

Do not take a double dose to make up for forgotten individual doses. Contact your doctor or pharmacist if needed.

4. POSSIBLE SIDE EFFECTS

[Description of side effects]

Like all medicines, PegIntron can have side effects. Although not all of these side effects may occur, they may need medical attention if they do.

The most common side effects are irritation or redness at the site of injection, weakness, dizziness or vertigo, tired feeling, fever, headache, flu-like symptoms, shaking chills, loss of weight, loss of appetite, nausea, diarrhoea or loose stools, stomach pain, muscle aches, pain in joints and muscles, feeling depressed, feeling anxious or nervous, difficulty concentrating, trouble falling asleep or staying asleep, irritability, hair loss, and sore throat.

Other common side effects that may occur are itching, dry skin, nervousness, feeling unwell, increased sweating, pain on the right side around your ribs, rash, vomiting, dry mouth, mood swings, breathing problems, virus infection, feeling sleepy, low thyroid gland activity (which may make you feel tired), chest pain, stomach upset, flushing, numbness or tingling feeling, coughing, agitation, sinusitis, tense muscles, increased or decreased sensitivity to touch, blurred vision, confusion, intestinal gas (flatus), loss of interest in sex, redness of skin, eye pain or infection, lack of interest in life, stuffy nose, constipation, difficult menstrual period.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems, confusion; feeling depressed, numbness or tingling feeling; trouble sleeping, thinking or concentrating; severe stomach pain; fever or chills beginning after a few weeks of treatment, pain in your lower back or side; problems with your eyesight or hearing; severe bleeding from your nose [your doctor will test your blood to ensure that your white blood cell (cells that fight infection) count and platelets (blood clotting cells) are at acceptable levels].

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING PEGINTRON

[Storage conditions and expiry date]

Keep out of the reach and sight of children

Store at 2°C - 8°C (in a refrigerator)

Do not use after the expiry date stated on the carton.

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored at 2°C - 8°C (in a refrigerator).

[Where appropriate, warning against certain visible signs of deterioration]

Do not use PegIntron if you notice discolouration of the powder.

This leaflet was last approved on

Further information

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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Nederland

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Deutschland

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2.1.1.1. Ελλάδα

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Suomi/Finland

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2.1.2. HOW TO SELF-INJECT PEGINTRON?

The following instructions explain how to inject PegIntron yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject PegIntron. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

2.2. Preparation

Collect necessary items before you begin:

- a vial of PegIntron powder for injection;
- an ampoule of solvent for PegIntron (water for injections);
- a 1 ml syringe;
- a long needle (for example 0.8 × 40 mm [21 gauge 1.5 inch]) to be used to add water for injections to the PegIntron powder vial;
- a short needle (for example 0.3 × 13 mm [30 gauge 0.5 inch]) for the subcutaneous injection;
- a cleansing swab.

Wash your hands carefully.

2.3. Reconstituting PegIntron powder for injection

Remove the protective cap from the PegIntron vial. Clean the rubber top of the vial with a cleansing swab. You can save the swab to clean the skin area where you will inject the dose. Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the long needle and place it firmly on to the tip of the syringe. Remove the needle guard without touching the needle and keep the syringe with the needle in your hand. Tap the top of the ampoule of solvent gently to make sure that all the liquid is at the bottom of the ampoule. Break off the top of the ampoule of solvent. Insert the needle in the ampoule of solvent and withdraw the total amount of solvent.

To prepare the PegIntron solution, insert the needle through the rubber top of the PegIntron vial and gently place the needle tip against the glass wall of the vial without touching the cleaned top of the vial with your hands.

Slowly inject the diluent, aiming the stream of liquid at the glass wall of the vial in order to avoid production of air bubbles. Do not aim the stream at the white powder at the bottom of the vial.

To dissolve the white contents, swirl the PegIntron vial with a gentle rotary motion leaving the syringe needle in the vial, until the contents are completely dissolved. **Do not shake**. If air bubbles do form, wait until the solution has settled and all bubbles have risen to the top of the solution and disappeared before withdrawing your dose from the vial. Use this solution immediately.

2.4. Measuring the dose of PegIntron from the reconstituted powder for injection

Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the PegIntron reconstituted solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw just more than the dose prescribed by your doctor into the syringe. Hold the syringe with the needle in the vial pointing up, remove the syringe from the long needle leaving the needle in the vial and without touching the tip of the syringe. Take the short needle and place it firmly on to the tip of the syringe. Remove the needle guard from the syringe needle and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing upwards, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Inspect visually the reconstituted solution prior to administration: do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

3.

3.1. Injecting the solution

Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.

Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand, hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of 45° to 90°. After the needle is in, remove the hand used to pinch the skin and use it to hold the syringe barrel. Pull back the plunger very slightly with one hand. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject into this site; withdraw the needle and repeat the procedure. Inject the solution by pushing the plunger all the way down gently.

Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.

The vial, ampoule and injection materials intended for single use must be discarded. Dispose of the syringe and needles safely in a closed container.

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

[Name of the medicinal product]

PegIntron 100 micrograms powder and solvent for solution for injection

peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol)

[Full statement of the active substance(s) and excipient(s)]

- The active substance is peginterferon alfa-2b, 100 micrograms/0.5 ml.
- The other ingredients are:
  Powder: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80;
  Solvent: water for injections 0.7 ml/ampoule.

[Name and address of the marketing authorisation holder and of the manufacturing authorisation holder responsible for batch release, if different]

Marketing Authorisation Holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

Manufacturer: SP (Brinny) Company, Innishannon, County Cork, Ireland

1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

[Pharmaceutical form and contents; pharmacotherapeutic group]

The pharmaceutical form is: powder and solvent for solution for injection.
The powder is contained in a 2 ml vial and the solvent is presented in a 2 ml ampoule.

Therapeutic indications

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used alone, in case of intolerance or contraindication to ribavirin to treat chronic hepatitis C, a viral infection of the liver.

The optimal treatment for chronic hepatitis C is the combination of interferon alfa-2b with ribavirin.

2. BEFORE YOU USE PEGINTRON

[List of information necessary before taking the medicinal product]

PegIntron is not recommended for use in patients under the age of 18 years.

[Contraindications]

Do not use PegIntron:

- If you are hypersensitive (allergic) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are hypersensitive (allergic) to any interferon.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have had a severe nervous or mental disorder.
- If you have thyroid disease that is not well controlled with medicines.
- If you have advanced, uncontrolled liver disease (other than hepatitis C).

- If you have severe kidney disease.
- If you have a condition that causes convulsions (seizures, or “fits”).
- If you are pregnant.

[Appropriate precautions for use; special warnings]

Take special care with PegIntron:

- If you ever had a heart attack or a heart problem.
- If you have had a problem with your liver (other than hepatitis C).
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- Be sure to tell your doctor if you are taking the Chinese herbal medication shosaikoto.

[[Use by pregnant or breast-feeding women]

Pregnancy

Ask your doctor or pharmacist for advice before taking any medicine. Do not use PegIntron during pregnancy. The effect on human pregnancy is not known.

Breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron.

[Effects on the ability to drive or to use machines]

Driving and using machines:

Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

[Interaction with other medicinal products]

Using other medicines:

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

3. HOW TO USE PEGINTRON

[Instructions for proper use]

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

[Dosage]

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

PegIntron is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year.

If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

[Method and/or route(s) of administration]

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to self-inject PegIntron at the end of the package leaflet).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if discolouration of the reconstituted solution is present. Discard any solution that is left in the vial after you give yourself the injection.

[Frequency of administration]

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

[Duration of treatment]

Use PegIntron exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take it for as long as prescribed.

[Symptoms in case of overdose and actions to be taken]

If you use more PegIntron than you should:

Tell your doctor or healthcare professional as soon as possible.

[Actions to be taken when one or more doses have been missed]

If you forget to take PegIntron:

Take the dose as soon as you remember, then continue your treatment as usual.

Do not take a double dose to make up for forgotten individual doses. Contact your doctor or pharmacist if needed.

4. POSSIBLE SIDE EFFECTS

[Description of side effects]

Like all medicines, PegIntron can have side effects. Although not all of these side effects may occur, they may need medical attention if they do.

The most common side effects are irritation or redness at the site of injection, weakness, dizziness or vertigo, tired feeling, fever, headache, flu-like symptoms, shaking chills, loss of weight, loss of appetite, nausea, diarrhoea or loose stools, stomach pain, muscle aches, pain in joints and muscles, feeling depressed, feeling anxious or nervous, difficulty concentrating, trouble falling asleep or staying asleep, irritability, hair loss, and sore throat.

Other common side effects that may occur are itching, dry skin, nervousness, feeling unwell, increased sweating, pain on the right side around your ribs, rash, vomiting, dry mouth, mood swings, breathing problems, virus infection, feeling sleepy, low thyroid gland activity (which may make you feel tired), chest pain, stomach upset, flushing, numbness or tingling feeling, coughing, agitation, sinusitis, tense muscles, increased or decreased sensitivity to touch, blurred vision, confusion, intestinal gas (flatus), loss of interest in sex, redness of skin, eye pain or infection, lack of interest in life, stuffy nose, constipation, difficult menstrual period.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems, confusion; feeling depressed, numbness or tingling feeling; trouble sleeping, thinking or concentrating; severe stomach pain; fever or chills beginning after a few weeks of treatment, pain in your lower back or side; problems with your eyesight or hearing; severe bleeding from your nose [your doctor will test your blood to ensure that your white blood cell (cells that fight infection) count and platelets (blood clotting cells) are at acceptable levels].

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING PEGINTRON

[Storage conditions and expiry date]

Keep out of the reach and sight of children

Store at 2°C - 8°C (in a refrigerator)

Do not use after the expiry date stated on the carton.

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored at 2°C - 8°C (in a refrigerator).

[Where appropriate, warning against certain visible signs of deterioration]

Do not use PegIntron if you notice discolouration of the powder.

This leaflet was last approved on

Further information

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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3.1.1.1. Ελλάδα

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3.1.2. HOW TO SELF-INJECT PEGINTRON?

The following instructions explain how to inject PegIntron yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject PegIntron. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

3.2. Preparation

Collect necessary items before you begin:

- a vial of PegIntron powder for injection;
- an ampoule of solvent for PegIntron (water for injections);
- a 1 ml syringe;
- a long needle (for example 0.8 × 40 mm [21 gauge 1.5 inch]) to be used to add water for injections to the PegIntron powder vial;
- a short needle (for example 0.3 × 13 mm [30 gauge 0.5 inch]) for the subcutaneous injection;
- a cleansing swab.

Wash your hands carefully.

3.3. Reconstituting PegIntron powder for injection

Remove the protective cap from the PegIntron vial. Clean the rubber top of the vial with a cleansing swab. You can save the swab to clean the skin area where you will inject the dose. Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the long needle and place it firmly on to the tip of the syringe. Remove the needle guard without touching the needle and keep the syringe with the needle in your hand. Tap the top of the ampoule of solvent gently to make sure that all the liquid is at the bottom of the ampoule. Break off the top of the ampoule of solvent. Insert the needle in the ampoule of solvent and withdraw the total amount of solvent.

To prepare the PegIntron solution, insert the needle through the rubber top of the PegIntron vial and gently place the needle tip against the glass wall of the vial without touching the cleaned top of the vial with your hands.

Slowly inject the diluent, aiming the stream of liquid at the glass wall of the vial in order to avoid production of air bubbles. Do not aim the stream at the white powder at the bottom of the vial.

To dissolve the white contents, swirl the PegIntron vial with a gentle rotary motion leaving the syringe needle in the vial, until the contents are completely dissolved. **Do not shake**. If air bubbles do form, wait until the solution has settled and all bubbles have risen to the top of the solution and disappeared before withdrawing your dose from the vial. Use this solution immediately.

3.4. Measuring the dose of PegIntron from the reconstituted powder for injection

Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the PegIntron reconstituted solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw just more than the dose prescribed by your doctor into the syringe. Hold the syringe with the needle in the vial pointing up, remove the syringe from the long needle leaving the needle in the vial and without touching the tip of the syringe. Take the short needle and place it firmly on to the tip of the syringe. Remove the needle guard from the syringe needle and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing upwards, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Inspect visually the reconstituted solution prior to administration: do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

4.

4.1. Injecting the solution

Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.

Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand, hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of 45° to 90°. After the needle is in, remove the hand used to pinch the skin and use it to hold the syringe barrel. Pull back the plunger very slightly with one hand. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject into this site; withdraw the needle and repeat the procedure. Inject the solution by pushing the plunger all the way down gently.

Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.

The vial, ampoule and injection materials intended for single use must be discarded. Dispose of the syringe and needles safely in a closed container.

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

[Name of the medicinal product]

PegIntron 120 micrograms powder and solvent for solution for injection

peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol)

[Full statement of the active substance(s) and excipient(s)]

- The active substance is peginterferon alfa-2b, 120 micrograms/0.5 ml.
- The other ingredients are:
  Powder: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80;
  Solvent: water for injections 0.7 ml/ampoule.

[Name and address of the marketing authorisation holder and of the manufacturing authorisation holder responsible for batch release, if different]

Marketing Authorisation Holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

Manufacturer: SP (Brinny) Company, Innishannon, County Cork, Ireland

1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

[Pharmaceutical form and contents; pharmacotherapeutic group]

The pharmaceutical form is: powder and solvent for solution for injection.
The powder is contained in a 2 ml vial and the solvent is presented in a 2 ml ampoule.

Therapeutic indications

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used alone, in case of intolerance or contraindication to ribavirin to treat chronic hepatitis C, a viral infection of the liver.

The optimal treatment for chronic hepatitis C is the combination of interferon alfa-2b with ribavirin.

2. BEFORE YOU USE PEGINTRON

[List of information necessary before taking the medicinal product]

PegIntron is not recommended for use in patients under the age of 18 years.

[Contraindications]

Do not use PegIntron:

- If you are hypersensitive (allergic) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are hypersensitive (allergic) to any interferon.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have had a severe nervous or mental disorder.
- If you have thyroid disease that is not well controlled with medicines.
- If you have advanced, uncontrolled liver disease (other than hepatitis C).

- If you have severe kidney disease.
- If you have a condition that causes convulsions (seizures, or “fits”).
- If you are pregnant.

[Appropriate precautions for use; special warnings]

Take special care with PegIntron:

- If you ever had a heart attack or a heart problem.
- If you have had a problem with your liver (other than hepatitis C).
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- Be sure to tell your doctor if you are taking the Chinese herbal medication shosaikoto.

[[Use by pregnant or breast-feeding women]

Pregnancy

Ask your doctor or pharmacist for advice before taking any medicine. Do not use PegIntron during pregnancy. The effect on human pregnancy is not known.

Breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron.

[Effects on the ability to drive or to use machines]

Driving and using machines:

Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

[Interaction with other medicinal products]

Using other medicines:

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

3. HOW TO USE PEGINTRON

[Instructions for proper use]

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

[Dosage]

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

PegIntron is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year.

If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

[Method and/or route(s) of administration]

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to self-inject PegIntron at the end of the package leaflet).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if discolouration of the reconstituted solution is present. Discard any solution that is left in the vial after you give yourself the injection.

[Frequency of administration]

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

[Duration of treatment]

Use PegIntron exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take it for as long as prescribed.

[Symptoms in case of overdose and actions to be taken]

If you use more PegIntron than you should:

Tell your doctor or healthcare professional as soon as possible.

[Actions to be taken when one or more doses have been missed]

If you forget to take PegIntron:

Take the dose as soon as you remember, then continue your treatment as usual.

Do not take a double dose to make up for forgotten individual doses. Contact your doctor or pharmacist if needed.

4. POSSIBLE SIDE EFFECTS

[Description of side effects]

Like all medicines, PegIntron can have side effects. Although not all of these side effects may occur, they may need medical attention if they do.

The most common side effects are irritation or redness at the site of injection, weakness, dizziness or vertigo, tired feeling, fever, headache, flu-like symptoms, shaking chills, loss of weight, loss of appetite, nausea, diarrhoea or loose stools, stomach pain, muscle aches, pain in joints and muscles, feeling depressed, feeling anxious or nervous, difficulty concentrating, trouble falling asleep or staying asleep, irritability, hair loss, and sore throat.

Other common side effects that may occur are itching, dry skin, nervousness, feeling unwell, increased sweating, pain on the right side around your ribs, rash, vomiting, dry mouth, mood swings, breathing problems, virus infection, feeling sleepy, low thyroid gland activity (which may make you feel tired), chest pain, stomach upset, flushing, numbness or tingling feeling, coughing, agitation, sinusitis, tense muscles, increased or decreased sensitivity to touch, blurred vision, confusion, intestinal gas (flatus), loss of interest in sex, redness of skin, eye pain or infection, lack of interest in life, stuffy nose, constipation, difficult menstrual period.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems, confusion; feeling depressed, numbness or tingling feeling; trouble sleeping, thinking or concentrating; severe stomach pain; fever or chills beginning after a few weeks of treatment, pain in your lower back or side; problems with your eyesight or hearing; severe bleeding from your nose [your doctor will test your blood to ensure that your white blood cell (cells that fight infection) count and platelets (blood clotting cells) are at acceptable levels].

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING PEGINTRON

[Storage conditions and expiry date]

Keep out of the reach and sight of children

Store at 2°C - 8°C (in a refrigerator)

Do not use after the expiry date stated on the carton.

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored at 2°C - 8°C (in a refrigerator).

[Where appropriate, warning against certain visible signs of deterioration]

Do not use PegIntron if you notice discolouration of the powder.

This leaflet was last approved on

Further information

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien

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Nederland

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Österreich

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4.1.1.1. Ελλάδα

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Suomi/Finland

PL 3/PB 3

FIN-02201 Espoo/Esbo

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Shire Park

Welwyn Garden City

Hertfordshire AL7 1TW - UK

Tel: + 44-(0)1 707 363 636

4.1.2. HOW TO SELF-INJECT PEGINTRON?

The following instructions explain how to inject PegIntron yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject PegIntron. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

4.2. Preparation

Collect necessary items before you begin:

- a vial of PegIntron powder for injection;
- an ampoule of solvent for PegIntron (water for injections);
- a 1 ml syringe;
- a long needle (for example 0.8 × 40 mm [21 gauge 1.5 inch]) to be used to add water for injections to the PegIntron powder vial;
- a short needle (for example 0.3 × 13 mm [30 gauge 0.5 inch]) for the subcutaneous injection;
- a cleansing swab.

Wash your hands carefully.

4.3. Reconstituting PegIntron powder for injection

Remove the protective cap from the PegIntron vial. Clean the rubber top of the vial with a cleansing swab. You can save the swab to clean the skin area where you will inject the dose. Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the long needle and place it firmly on to the tip of the syringe. Remove the needle guard without touching the needle and keep the syringe with the needle in your hand. Tap the top of the ampoule of solvent gently to make sure that all the liquid is at the bottom of the ampoule. Break off the top of the ampoule of solvent. Insert the needle in the ampoule of solvent and withdraw the total amount of solvent.

To prepare the PegIntron solution, insert the needle through the rubber top of the PegIntron vial and gently place the needle tip against the glass wall of the vial without touching the cleaned top of the vial with your hands.

Slowly inject the diluent, aiming the stream of liquid at the glass wall of the vial in order to avoid production of air bubbles. Do not aim the stream at the white powder at the bottom of the vial.

To dissolve the white contents, swirl the PegIntron vial with a gentle rotary motion leaving the syringe needle in the vial, until the contents are completely dissolved. **Do not shake**. If air bubbles do form, wait until the solution has settled and all bubbles have risen to the top of the solution and disappeared before withdrawing your dose from the vial. Use this solution immediately.

4.4. Measuring the dose of PegIntron from the reconstituted powder for injection

Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the PegIntron reconstituted solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw just more than the dose prescribed by your doctor into the syringe. Hold the syringe with the needle in the vial pointing up, remove the syringe from the long needle leaving the needle in the vial and without touching the tip of the syringe. Take the short needle and place it firmly on to the tip of the syringe. Remove the needle guard from the syringe needle and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing upwards, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Inspect visually the reconstituted solution prior to administration: do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

5.

5.1. Injecting the solution

Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.

Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand, hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of 45° to 90°. After the needle is in, remove the hand used to pinch the skin and use it to hold the syringe barrel. Pull back the plunger very slightly with one hand. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject into this site; withdraw the needle and repeat the procedure. Inject the solution by pushing the plunger all the way down gently.

Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.

The vial, ampoule and injection materials intended for single use must be discarded. Dispose of the syringe and needles safely in a closed container.

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

[Name of the medicinal product]

PegIntron 150 micrograms powder and solvent for solution for injection

peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol)

[Full statement of the active substance(s) and excipient(s)]

- The active substance is peginterferon alfa-2b, 150 micrograms/0.5 ml.
- The other ingredients are:
  Powder: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80;
  Solvent: water for injections 0.7 ml/ampoule.

[Name and address of the marketing authorisation holder and of the manufacturing authorisation holder responsible for batch release, if different]

Marketing Authorisation Holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

Manufacturer: SP (Brinny) Company, Innishannon, County Cork, Ireland

1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

[Pharmaceutical form and contents; pharmacotherapeutic group]

The pharmaceutical form is: powder and solvent for solution for injection.
The powder is contained in a 2 ml vial and the solvent is presented in a 2 ml ampoule.

Therapeutic indications

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used alone, in case of intolerance or contraindication to ribavirin to treat chronic hepatitis C, a viral infection of the liver.

The optimal treatment for chronic hepatitis C is the combination of interferon alfa-2b with ribavirin.

2. BEFORE YOU USE PEGINTRON

[List of information necessary before taking the medicinal product]

PegIntron is not recommended for use in patients under the age of 18 years.

[Contraindications]

Do not use PegIntron:

- If you are hypersensitive (allergic) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are hypersensitive (allergic) to any interferon.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have had a severe nervous or mental disorder.
- If you have thyroid disease that is not well controlled with medicines.
- If you have advanced, uncontrolled liver disease (other than hepatitis C).

- If you have severe kidney disease.
- If you have a condition that causes convulsions (seizures, or “fits”).
- If you are pregnant.

[Appropriate precautions for use; special warnings]

Take special care with PegIntron:

- If you ever had a heart attack or a heart problem.
- If you have had a problem with your liver (other than hepatitis C).
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- Be sure to tell your doctor if you are taking the Chinese herbal medication shosaikoto.

[[Use by pregnant or breast-feeding women]

Pregnancy

Ask your doctor or pharmacist for advice before taking any medicine. Do not use PegIntron during pregnancy. The effect on human pregnancy is not known.

Breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron.

[Effects on the ability to drive or to use machines]

Driving and using machines:

Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

[Interaction with other medicinal products]

Using other medicines:

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

3. HOW TO USE PEGINTRON

[Instructions for proper use]

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

[Dosage]

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

PegIntron is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year.

If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

[Method and/or route(s) of administration]

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to self-inject PegIntron at the end of the package leaflet).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if discolouration of the reconstituted solution is present. Discard any solution that is left in the vial after you give yourself the injection.

[Frequency of administration]

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

[Duration of treatment]

Use PegIntron exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take it for as long as prescribed.

[Symptoms in case of overdose and actions to be taken]

If you use more PegIntron than you should:

Tell your doctor or healthcare professional as soon as possible.

[Actions to be taken when one or more doses have been missed]

If you forget to take PegIntron:

Take the dose as soon as you remember, then continue your treatment as usual.

Do not take a double dose to make up for forgotten individual doses. Contact your doctor or pharmacist if needed.

4. POSSIBLE SIDE EFFECTS

[Description of side effects]

Like all medicines, PegIntron can have side effects. Although not all of these side effects may occur, they may need medical attention if they do.

The most common side effects are irritation or redness at the site of injection, weakness, dizziness or vertigo, tired feeling, fever, headache, flu-like symptoms, shaking chills, loss of weight, loss of appetite, nausea, diarrhoea or loose stools, stomach pain, muscle aches, pain in joints and muscles, feeling depressed, feeling anxious or nervous, difficulty concentrating, trouble falling asleep or staying asleep, irritability, hair loss, and sore throat.

Other common side effects that may occur are itching, dry skin, nervousness, feeling unwell, increased sweating, pain on the right side around your ribs, rash, vomiting, dry mouth, mood swings, breathing problems, virus infection, feeling sleepy, low thyroid gland activity (which may make you feel tired), chest pain, stomach upset, flushing, numbness or tingling feeling, coughing, agitation, sinusitis, tense muscles, increased or decreased sensitivity to touch, blurred vision, confusion, intestinal gas (flatus), loss of interest in sex, redness of skin, eye pain or infection, lack of interest in life, stuffy nose, constipation, difficult menstrual period.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems, confusion; feeling depressed, numbness or tingling feeling; trouble sleeping, thinking or concentrating; severe stomach pain; fever or chills beginning after a few weeks of treatment, pain in your lower back or side; problems with your eyesight or hearing; severe bleeding from your nose [your doctor will test your blood to ensure that your white blood cell (cells that fight infection) count and platelets (blood clotting cells) are at acceptable levels].

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING PEGINTRON

[Storage conditions and expiry date]

Keep out of the reach and sight of children

Store at 2°C - 8°C (in a refrigerator)

Do not use after the expiry date stated on the carton.

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored at 2°C - 8°C (in a refrigerator).

[Where appropriate, warning against certain visible signs of deterioration]

Do not use PegIntron if you notice discolouration of the powder.

This leaflet was last approved on

Further information

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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5.1.1.1. Ελλάδα

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HOW TO SELF-INJECT PEGINTRON?

The following instructions explain how to inject PegIntron yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject PegIntron. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation

Collect necessary items before you begin:

- a vial of PegIntron powder for injection;
- an ampoule of solvent for PegIntron (water for injections);
- a 1 ml syringe;
- a long needle (for example 0.8 × 40 mm [21 gauge 1.5 inch]) to be used to add water for injections to the PegIntron powder vial;
- a short needle (for example 0.3 × 13 mm [30 gauge 0.5 inch]) for the subcutaneous injection;
- a cleansing swab.

Wash your hands carefully.

Reconstituting PegIntron powder for injection

Remove the protective cap from the PegIntron vial. Clean the rubber top of the vial with a cleansing swab. You can save the swab to clean the skin area where you will inject the dose. Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the long needle and place it firmly on to the tip of the syringe. Remove the needle guard without touching the needle and keep the syringe with the needle in your hand. Tap the top of the ampoule of solvent gently to make sure that all the liquid is at the bottom of the ampoule. Break off the top of the ampoule of solvent. Insert the needle in the ampoule of solvent and withdraw the total amount of solvent.

To prepare the PegIntron solution, insert the needle through the rubber top of the PegIntron vial and gently place the needle tip against the glass wall of the vial without touching the cleaned top of the vial with your hands.

Slowly inject the diluent, aiming the stream of liquid at the glass wall of the vial in order to avoid production of air bubbles. Do not aim the stream at the white powder at the bottom of the vial.

To dissolve the white contents, swirl the PegIntron vial with a gentle rotary motion leaving the syringe needle in the vial, until the contents are completely dissolved. **Do not shake**. If air bubbles do form, wait until the solution has settled and all bubbles have risen to the top of the solution and disappeared before withdrawing your dose from the vial. Use this solution immediately.

Measuring the dose of PegIntron from the reconstituted powder for injection

Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the PegIntron reconstituted solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw just more than the dose prescribed by your doctor into the syringe. Hold the syringe with the needle in the vial pointing up, remove the syringe from the long needle leaving the needle in the vial and without touching the tip of the syringe. Take the short needle and place it firmly on to the tip of the syringe. Remove the needle guard from the syringe needle and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing upwards, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Inspect visually the reconstituted solution prior to administration: do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution

Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.

Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand, hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of 45° to 90°. After the needle is in, remove the hand used to pinch the skin and use it to hold the syringe barrel. Pull back the plunger very slightly with one hand. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject into this site; withdraw the needle and repeat the procedure. Inject the solution by pushing the plunger all the way down gently.

Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.

The vial, ampoule and injection materials intended for single use must be discarded. Dispose of the syringe and needles safely in a closed container.